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DRUG COMBINATIONS OBTAINED FROM ALPHA-LIPOIC ACID AND CARDIOVASCULAR-ACTIVE SUBSTANCES [ARZNEIMITTELKOMBINATIONEN AUS ALPHA-LIPONSÄURE UND HERZ-KREISLAUFAKTIVEN SUBSTANZEN]

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Description

The invention relates to pharmaceutical combination preparations consisting of alpha-lipoic acid, dihydrolipoic acid and their oxidized or reduced R- or S-enantiomers as well as metabolites of alpha-lipoic acid and at least an organic nitrate, calcium- antagonists or ACE-inhibitors.

Alpha-lipoic acid, chemically seen, is 1,2- dithia-cyclopentane-3- valerianic acid.

It is widely used in plants and animals in the form of R-enantiomer and acts as a co-enzyme in many enzymatic reactions, represents a growth factor for some bacteria and protozoa and is used for amanita phalloides poisoning. Further, alpha-lipoic acid- racemate has antiphlogistic, antinociceptive (analgesic) as well as cyto-protective, neuro-protective, antiallergic and anti-tumor properties (refer to DE 40 35 442 A1).

The purely optical enantiomers of alpha-lipoic acid (R- and S-form, that means R-alpha- lipoic acid and S-alpha- lipoic acid) have special effects when compared to the racemate.

It is known that R-enantiomer is effective predominantly as antiphlogistic and the S-enantiomer as predominantly antinociceptive. The antiphlogistic effect of

R-enantiomer is about 10 times stronger than that of racemate.

The antinociceptive (analgesic) effect of S-enantiomer is for example, 6 times stronger than that of racemate. Therefore, the enantiomers represent active substances that are much more specific and stronger when compared to the racemate (refer to DE 40 35 442 A1).

/2 Numbers in the margin indicate the pagination in the foreign text.

The therapeutically important organic nitrates are esters of nitrous acid and nitric acid such as amylnitrite, nitroglycerine, isosorbitdinitrate or 5-isosorbitmononitrate. The basic effect of nitrites and organic nitrates is the relaxation of smooth musculature (effective mechanism of organic nitrate refer to Forth, Henschler, Rummel in: Pharmacology and toxicology, Scientific journal, Mannheim, Wien, Zurich, 5th edition 1990, Pages 268 onwards).

It is known that

- the effect of nitrites and organic nitrates on smooth musculature is linked to the availability of SH-groups
- the S-nitrosothiols bring about relaxation of coronary vascular streaks

- the instability of S-nitrosothiols correspond to the duration of effect of organic nitrates in their chronological sequence in case of i.v. administration and
- Slowdown of effectiveness was observed in spite of constant dosage during continuous therapy leading to so-called nitrate tolerance, above all, during retard- preparations in higher dosage and for transdermal administration with persistently high organic nitrate blood levels.

Calcium - antagonists as combination partners are Verapamil, nifedipine, nimodipine, felodipine, isradipine, nitrendipine, nisoldipine, nicardipine, nivaldipine and diltiazem. Use of calcium antagonists, nimodipine for fighting against impairments of peripheral nerves that were caused due to diabetes, were already described in DE 41 25 116 A1.

ACE- inhibitors of the type of captopril, lisinopril, perindropril-tert-butylamine, ramipril and enalapril hydrogen maleate can be used as other combination partners.

ACE- inhibitors are angiotensin-converting- enzyme-inhibitors; they are compounds whose effect is based on the hindrance of splitting of a peptide bond of angiotensin I in the vascoconstricting angiotensin II.

Thus, a decrease in systemic resistance and increase in cardiac output and decrease in left-ventricular and right-ventricular filling pressure are caused.

Oxyfedrin can be used as another combination partner. Oxyfedrin is an aminoketone obtained from the phenylethylamine- series (oxyfedrine = L-3- (β-hydroxy-alpha-methylphenethylamino)- 3'-methoxy-propiophenone-hydrochloride). The cardio-energetic coronary effect of Oxyfedrine lies in improvement of coronary- and myocardial blood supply and increase in stroke volume and minute volume, whereby the cardiodynamic changes are correlated in each phase to optimum energy preparation and energy utilization.

The objective of the present invention is to make available combination preparations with synergetic effect for improved treatment of especially cardio-circulatory disorders as well as diseases caused due to diabetes.

It is achieved according to the invention in that pharmaceutical combination preparations, consisting of alpha-lipoic acid, dihydrolipoic acid and their oxidized or reduced R- or S-enantiomers as well as metabolites of alpha- lipoic acid, such as 6,8- bisnorlipoic acid, tetranorlipoic acid (active substance A) and at least an

organic nitrate, calcium- antagonists, ACE- inhibitors or oxyfedrine, are used.

For example, glyceroltri- nitrate, isosorbitdinitrate or 5-isosorbitmononitrate can be used as organic nitrates.

Verapamil, nifedipine, nimodipine, felodipine, isradipine, nitrendipine, nisoldipine, nicardipine, nivaldipine and diltiazem are suitable as calcium-antagonists.

Those of the type of captopril, lisinopril, perindropril-tert-butylamine, ramipril and enalapril hydrogen maleate can be used as ACE- inhibitors.

Surprisingly, it was found that stronger effects were obtained in the combination of say, glyceroltri- nitrate, isosorbitdinitrate or 5-isosorbitmononitrate with purely optical enantiomers of alpha- lipoic acid when compared to the racemate of alpha-lipoic acid alone.

/3

The combination of isosorbitdi-nitrate with S-enantiomer of alpha- lipoic acid shows vascular-relaxing effect and the R-enantiomer in combination with glyceroltri-nitrate shows anti-ischemic effect, whereby, surprisingly, the anti-ischemic effect of R-enantiomer in combination with 5-isosorbitmononitrate is stronger than

that of racemate of alpha- lipoic acid. The anti-ischemic effect of R-enantiomers in combination with isosorbitdi-nitrate is likewise stronger than that of racemate of alpha- lipoic acid. The enantiomers of alpha-lipoic acid in combination with organic nitrates such as glyceroltri-nitrate, isosorbitdinitrate or 5-isosorbitmononitrate, have active substances that are more specific and stronger when compared to the racemate of alpha- lipoic acid.

It was even more surprising that in the combination of active substances of Claim 3 such as the nitrates, say, glyceroltrinitrate, isosorbitdinitrate or 5-isosorbitmononitrate with the purely optical isomers of alpha- lipoic acid (R- and S-form, that means R-alpha-lipoic acid and S-alpha- lipoic acid) when compared to the organic nitrates alone, surprisingly, vascular-relaxing effect was found in the combination with say, the nitrate, isosorbitdintrate with R-enantiomer and the R-enantiomer is effective as anti-ischemic in combination with the nitrate, glyceroltrinitrate, whereby, surprisingly, the anti-ischemic effect of R-enantiomers in combination with nitrates, such as 5-isosorbitmononitrate, is stronger than that of the respective organic nitrate alone. The anti-ischemic effect of R-enantiomers in combination with nitrate such as isosorbitdintrate is say, stronger than

that of isosorbitdintrate. The enantiomers of alpha- lipoic acid in combination with nitrates such as glyceroltrinitrate, isosorbitdinitrate or 5-isosorbitmononitrate have much more specific and stronger active substances when compared to the organic nitrates of Claim 3.

The combinations with the organic nitrates according to the invention like, for e.g. glyceroltrinitrate, isosorbitdinitrate or 5-isosorbitmononitrate and the optical enantiomers of alpha-lipoic acid exhibit a good coronary- relaxing, anti-ischemic, cardiac insufficiency-therapeutic or anti-organic nitrate tolerance- effect in the following trial models:

1) in vitro: isolated guinea pig- rabbit aorta or isolated right or left auricle of guinea pig
2) in vivo: dog, domestic pig, model: coronary stenosis with the help of balloon-tipped catheter methods with subsequent, histological trial for reducing size of infarction or occurrence of infarction.

The pharmaceutical combination preparations consisting of active substances A and an organic nitrate, generally contain between 1 mg to 1.2 g as single dose, preferably 2 mg to 800 mg of R- or S-alpha- lipoic acid in combination with preferably 0.1 -40 mg of organic nitrate, such as for

e.g. glyceroltrinitrate, isosorbitdinitrate or 5-isosorbitmononitrate.

The obtained effective ranges per kg of body weight must lie between 1.5 and 200 mg, preferably between 4 and 100 mg for R- or S-alpha- lipoic acid in the combination according to the invention, and must lie between 0.1 - 40 mg, preferably 0.8 - 20 mg for the organic nitrates, like, say glyceroltrinitrate, isosorbitdinitrate or 5-isosorbitmononitrate.

Likewise, it was surprisingly found that stronger effects were obtained in the combination of calcium-antagonists, for e.g. Verapamil, with purely optical enantiomers of alpha-lipoic acid when compared to the racemate of alpha-lipoic acid alone. The combination with say, calcium- antagonists, verapamil with R- enantiomers shows anti-diabetic effect, i.e. blood sugar-decreasing effect and the R-enantiomer in combination with calcium-antagonists, nimodipin, shows neurocytoprotective effect. The neuroprotective effect of R- enantiomer in combination with calcium- antagonists, nimodipin, is stronger than that of the racemate of alpha- lipoic acid. The anti-hypertensive effect of R- enantiomer in combination with calcium- antagonists, nimodipin or nifedipin is, likewise, stronger than that of the racemate of alpha- lipoic acid.

The enantiomers of alpha- lipoic acid in combination with nifedipin constitute very much specific and stronger effective active substances when compared with the racemate of alpha- lipoic acid.

It was surprisingly found that in the combination of active substances of Claim 4 like, for e.g., calcium antagonists, Verapamil with purely optical R-isomers of alpha-lipoic acid when compared to Verapamil alone, surprisingly, it was more anti-diabetic, i.e. it had blood sugar- reducing effect in the combination and the R-enantiomer in combination with calcium-antagonists, nimodipin, shows stronger neurocytoprotective effect than nimodipin alone.

The anti-hypertensive effect of R-enantiomer in combination with calcium antagonists, nifedipin, is stronger than that of nifedipin alone. The enantiomers in combination with the calcium- antagonists of the type verapamil, nifedipine, nimodipine, felodipine, isradipine, nitrendipine, nisoldipine, nicardipine, nivaldipine and diltiazem constitute much more specific and stronger effective substances when compared to the calcium antagonists of Claim 4 alone.

The pharmaceutical preparations of combinations of active substances A with at least one calcium- antagonist generally contain between 1 mg to 3 g as single dose, preferably 2 mg to 1.2 g of R- or S-alpha- lipoic acid in combination with 1 to 120 mg of a calcium- antagonist.

The obtained effective ranges per 1 kg of body weight must lie between 1.5 and 200 mg, preferably between 4 and 100 mg for R- or S-alpha- lipoic acid in the combination according to the invention, and must lie between 1 - 120, preferably between 5- 90 mg for the calcium- antagonist.

Further, it was surprisingly found that stronger blood sugar-reducing effects occur in the combination with ACE-inhibitors, like Captopril, with the purely optical R-enantiomer of alpha- lipoic acid when compared to the racemate of alpha- lipoic acid and stronger cardio-cytoprotective effects occur with the R-enantiomer in combination with ACE-inhibitor, enalapril hydrogen maleate. The cardio-cytoprotective effect of enantiomer in combination with ACE-inhibitor, enalapril hydrogen maleate, is stronger than that of the racemate of alpha- lipoic acid.

/4

The anti-hypertensive effect of R- enantiomer in combination with the ACE-inhibitor, ramipril, is likewise, stronger than that of the racemate of alpha- lipoic acid.

The enantiomers of alpha- lipoic acid in combination with the ACE-inhibitors of the type captopril, lisinopril, perindropril-tert-butylamine, ramipril, enalapril hydrogen maleate constitute much more specific and stronger effective substances when compared to the racemate of alpha- lipoic acid.

It was surprisingly found that vascular-relaxing effect was obtained with the R-enantiomer surprisingly in combination with, say, the ACE-inhibitor, Captopril in combination of active substances of Claim 5 as with the ACE-inhibitors, such as captopril, ramipril and enalapril hydrogen maleate with the purely optical isomers of alpha-lipoic acid (R- and S-form, that means R-alpha- lipoic acid and S-alpha- lipoic acid) when compared to the organic ACE-inhibitors alone and the R-enantiomer in combination with the nitrate, glyceroltrinitrate is cardiocytoprotective, whereby, surprisingly, the cardiocytoprotective effect of R- enantiomer in combination with ACE-inhibitor such as for e.g. captopril, is stronger than that of captopril alone. The cardiocytoprotective effect of R-enantiomer in combination with ACE-inhibitor such as say captopril, is

stronger than that of captopril alone. The enantiomers of alpha-lipoic acid in combination with ACE-inhibitors such as captopril, ramipril, lisinopril and enalapril hydrogen maleate, therefore, constitute much more specific and stronger effective substances when compared to the ACE-inhibitors of Claim 5.

The effects of combinations of the invention with ACE-inhibitors were investigated with the following trial models:

1) in vitro: isolated guinea pig- rabbit aorta or isolated right or left auricle of guinea pig
2) in vivo: dog, domestic pig, model: coronary stenosis with the help of balloon-tipped catheter methods with subsequent, histological trial for reducing size of infarction or occurrence of infarction.
3) Test model for cardio-cytoprotective effect

For instance, the S- enantiomer (S- alpha-lipoic acid) in combination with ACE- inhibitor, captopril, shows a synergistic, prophylactic and therapeutic effect of

combination pointing to the vascular-relaxing effect on humans and isolated guinea pig aorta which can be thought of for those of alpha- lipoic acid alone or the ACE-inhibitor alone (peroral application).

4) Testing of anti-arteriosclertoic effect

Scalbert et al: Journal of Cardiovascular Pharmacology 18 (Suppl. 7) Page 25 - Page 32 1991

5) Test model for anti-hypertensive effect

(Model refer also: Nagano et al.: Journal of Hypertension 1991, 9; 595- 599

For instance, the S-enantiomer in combination with ACE- inhibitor, lisinopril, shows a synergistic, prophylactic and therapeutic effect of combination pointing to hypertension in spontaneously- hypertensive rats, which can be thought of for those of alpha-lipoic acid (that means the racemate) or the ACE-inhibitor alone (peroral application). Likewise, an anti-hypertensive effect was observed in animal trials for the oxidized or reduced R- and S-form of alpha- lipoic acid in combination with ACE-inhibitor, enalapril, already from a dose of 20 mg/kg of R- or S-enantiomer or alpha- lipoic acid in combination with 10 mg/kg of ACE-inhibitor by mouth.

6) Test model for anti-diabetic effect

Streptozotocin- induced diabetes in rats. Study of glucose assimilation in muscles after pre-treatment of rats with the combination.

7) Testing for acute cell toxicity in fibroblasts of mouse, L 929 or the like. According to LINDL et al.

in: Cell and tissue culture, Gustav Fischer Verlag, Stuttgart, New York, 2nd Edition, 1989, Pages 164- 167.

8) Testing for influence of substance on metabolic activity

According to LINDL et al. in: Cell and tissue culture, Gustav Fischer Verlag, Stuttgart, New York, 2nd Edition, 1989, Pages 167- 168.

The combination of active substances A with ACE-inhibitors shows a good effect on metabolic activity in the following trial models:

- rats –or guinea pig aorta- model
- in-vitro model: Isolated aorta of rats or guinea pigs with prophylactic administration of test substances

For methods, refer also: Tian et al: European Journal of Pharmacology, 203, (1991) 71- 77

9) Testing for anti-arteriosclerotic effect

Scalbert et al.: Journal of Cardiovascular Pharmacology 18 (Suppl. 7) Page 25- 32, 1991.

The pharmaceutical combination preparations consisting of the active substance A and at least one ACE-inhibitor generally contain between 1 mg to 3 g as

single dose, preferably 2 mg to 1.2 g of R- or S-alpha-lipoic acid and for instance, 1 to 18 mg of captopril.

/5

The active substances must be released from the preparations slowly.

Preferred forms of usage are for e.g., tablets that contain between 5 mg and 500 mg or solutions that contain between 5 mg to 0.2 g/ml of fluid of active substances.

Further, it was found surprisingly that vascular-relaxing effect was found with R-enantiomer in combination with oxyfedrin in the combination of oxyfedrin with purely optical isomers of alpha-lipoic acid (R- and S-form, that means R-alpha-lipoic acid and S-alpha-lipoic acid) when compared to the racemate of alpha-lipoic acid alone and the R-enantiomer in combination with oxyfedrin is effective as an anti-ischemic, whereby, surprisingly, the anti-ischemic effect of R-enantiomer in combination with oxyfedrin is likewise stronger than that of the racemate of alpha-lipoic acid. The anti-ischemic effect of R-enantiomer in combination with oxyfedrin is likewise stronger than that of racemate of alpha- lipoic acid.

The enantiomers of alpha-lipoic acid in combination with oxyfedrin, therefore, constitute much more specific

and stronger active substances when compared to the racemate of alpha- lipoic acid.

Preferably, the salts with pharamaceutically usable halogens are used in aqueous solutions.

The application of combination preparations consisting of active substance A and at least one organic nitrate, calcium- antagonists, ACE-inhibitors or oxyfedrin can be undertaken on the skin or mucous membrane or inside the body, for example, orally, enteral, pulmonal, nasal, lingual, intravenous, intra-arterial, intra-cardial, intra-muscular, intra-peritoneal, intracutaneous, subcutaneous. It concerns sterile or sterilized products in case of parenteral administration.

Therefore, the administration can be undertaken in the form of tablets, capsules, pills, sugar-coated pills, aerosols, salves, creams, medical strips or in fluid form, whereby the active substances can be combined, if necessary, with known excipients.

The fluid forms of administration can be: alcoholic or aqueous solutions as well as suspensions and emulsions.

Salts with pharmaceutically usage halogens are preferably used in aqueous solutions.

The customary bases or cations can be used as halogens which are physiologically compatible in the salt form. Examples for the same are alkali metals or alkaline- earth metals, ammonium hydroxide, alkaline amino acids such as arginine and lysine, amines of formula N R_1 R_2 R_3 wherein the radicals R_1 R_2 and R_3 are same or different and hydrogen, C_1 - C_4- alkyl or C_1 - C_4- oxyalkyl mean mono and diethanolamine, 1-amino-2-propanol, 3- amino-1- propanol; alkylene diamine with an alkylene chain made from 2 to 6 C-atoms such as ethylene diamine or hexamethylene tetramine, saturated cyclic amino compounds with 4 - 6 ring carbon atoms such as piperidine, piperazine, pyrrolidine, morpholine, N-methyl glucamine, creatine, trometamol.

/6

Table 1

Examples for oral doses of combination preparations with organic nitrates for therapy of angina pectoris in humans

Organic nitrate	Active substance A	Daily dosage of organic nitrate	Daily dosage of active substance A	Single dosage a) organic nitrate b) Active substance A	Frequency of application
Glycerol-	Oxidized/	0.8-	300-1200	a) 0.8 -	1-3

trinitrate	reduced racemate or R- or S-alpha-lipoic acid	6.5 mg/d	mg	6.5 mg b) 100-400 mg	
Isosorbit-dinitrate	Oxidized/ reduced racemate or R- or S-alpha-lipoic acid	10- 30 mg/d	300-1200 mg	a) 2.5 - 10 mg b) 100-400 mg	1- 3
Isosorbit mono-nitrate	Oxidized/ reduced racemate or R- or S-alpha-lipoic acid	20- 80 mg/d	300-1200 mg	a) 10 - 40 mg b) 100-400 mg	1- 2

The single dose of active substance A in the combination with organic nitrates can contain the following for R-enantiomer of alpha- lipoic acid:

a) for oral administration between 5 - 300 mg, preferably 30 mg -240 mg, especially 30 mg - 150 mg

b) for parenteral administration (for e.g. intravenous, intramuscular) between 10 - 250 mg, preferably 20 mg - 150 mg, especially 30- 90mg.

The doses can be administered daily once to 4 times, preferably 1- 2 times. The daily dosage of R- or S-alpha-lipoic acid in combination with organic nitrates can be 2-

40mg/kg weight for humans, whereby this dose is administered up to 4 times per day.

The daily dose can be for instance, 100 - 600 mg. Therefore, the drugs preferably contain 100 - 600 mg of R- or S- alpha-lipoic acid in a galenic formulation, whereby such a dose is preferably administered up to 3 times.

The single dose of organic nitrates in the combination preparations can lie for instance:

a) for oral administration between 5mg - 40 mg, preferably 10 mg.

b) for inhalation (solutions of aerosols) between 0.100 mg - 1.2 mg, preferably 0.41 mg - 1 mg.

In case the organic nitrate such as glyceroltri-nitrate, isosorbitdi-nitrate or 5-isosorbitmono-nitrate is used for instance, in combination with R- or S-alpha-lipoic acid in the form of its salts, the halogen can be used even in excess, that means, in a higher quantity than equimolar quantity.

/7

Table 2

Example for oral doses of combination preparations with calcium-antagonists for the therapy of different indications in humans

Substance of Claim 2	Substance of Claim 1	Daily dose of substance of claim 2	Daily dose of substance of claim 1	Single dose of substance of a) claim 2 b) claim 1	Frequency of application	Indication
Nifedipin	Oxidized/ reduced racemate or R- or S-enantiomer of alpha-lipoic acid	5-30 mg/day	300 mg- 1.2 g	a) 5-10 mg b) 100 mg - 400 mg	1-3	Angina pectoris, hypertension
Verapamil	Oxidized/ reduced racemate or R- or S-enantiomer of alpha-lipoic acid	40- 360 mg/day	300 mg- 1.2 g	a) 40 mg - 120 mg b) 100 mg- 400 mg	1- 3	Tachycardia, atrial fibrillation, ischemic-ventricular extrasystole after myocardial infarction, coronary-insufficiency
Nimodipin	Oxidized/ reduced racemate or R- or S-enantiomer of alpha-lipoic acid	30- 90 mg/day	300 mg- 1.2 g	a) 10 mg - 30 mg b) 100 mg - 400 mg	1- 3	Neuropathy, cerebral neuropathy
Diltiazem	Oxidized/ reduced racemate or R- or S-enantiomer of alpha-lipoic acid	60- 180 mg/day	300 mg- 1.2 g	20- 60 mg b) 100 mg- 400 mg	1-3	Coronary heart disease, coronary spasm, atrial fibrillation
Felodipin	Oxidized/	5-10	300 mg-	a) 5 mg-	1	Angina

	reduced racemate or R- or S- enantiomer of alpha- lipoic acid	mg/day	1.2 g	10 mg b) 100 mg- 400 mg		pectoris, myocardial infarction, hypertension, coronary heart disease
Nisoldipin	Racemate or R- or S- enantiomer of alpha- lipoic acid	5- 10mg/day	250 mg- 1.2 g	a) 10 mg - 20mg b) 60 mg - 400 mg	1-2	Coronary heart disease, hypertension, angina pectoris

/8

The single dose of active substance A in combination, for instance, with calcium- antagonist, nimodipin, can lie:

a) for oral administration between 50 mg - 3g, preferably 100 mg - 1.2 g, especially 300- 600 mg.

b) for parenteral administration (for e.g. intravenous, intramuscular) between 50 mg - 2 g, preferably 100 mg - 3 g, especially 300 - 600 mg.

c) for inhalation (solutions or aerosols) between 0.010 mg - 1.2 g, preferably 0.020 mg- 600 mg, especially 0.5 - 300 mg.

The doses can be administered one to four times, preferably one to three times daily or even as continuous infusion with the help of infusionates.

The daily dose of R- or S-alpha- lipoic acid in combination with nimodipin can lie at 2- 40 mg per kg of

weight in humans, the single dose being 1- 10 mg per kg of weight.

The daily dose can be preferably 100 - 600 mg, therefore, the drugs contain 100- 600 mg of R- or S- alpha-lipoic acid in a galenic formulation, whereby such a dose is administered preferably up to 4 times.

For the treatment, say 1 to 3 tablets with a content of 5 mg to 2 g of the active substance A can be given daily or say, an ampoule/ infusion bottle of 1 to 100 ml of content with 500 mg to 6 g of active substance A in combination with 1 mg - 20 mg of a calcium-antagonist is recommended daily one to four times in case of intravenous injection.

In case of oral administration, the minimum daily dose of active substance A in combination with a calcium-antagonist is, say, 200 mg; the maximum daily dose should not exceed 1 g.

The single dose of a calcium-antagonist, such as nimodipin, in combination with R- or S- enantiomer of alpha-lipoic acid, can lie at:

a) for oral administration between 30 - 90 mg, preferably 10 mg - 80 mg, especially 30- 60 mg.
b) for parenteral administration (for e.g. intravenous) about 15 micrograms/ kg of body weight/ hour every hour.

The daily oral dose of calcium-antagonist, nimodipin, in combination with the oxidized or reduced racemate or R- or S-enantiomer of alpha- lipoic acid can lie at 0.05- 1.2 mg/ per kg of body weight in humans, the single dose of nimodipin in this combination is at 0.005 - 0.04 mg per kg of body weight, whereby this dose is administered suitably up to three times a day.

For the treatment, 1 to 2 tablets with a content of 1 mg to 30 mg of nimodipin can be given daily three times for the calcium- antagonist, nimodipin in the combination of the invention or say, an ampoule/ infusion bottle of 10 to 50 ml of content with 0.10 mg to 10 mg of nimodipin is recommended daily one to three times in case of intravenous injection.

In case of oral administration, the minimum daily dose for nimodipin in combination is 30 mg; however, the maximum daily dose should not exceed 360 mg.

Preferred forms of administration of combination partner A with nimodipin are for e.g. tablets that lie between 10 mg and 2 g or solutions that contain between 10 mg to 0.2 g/ml of fluid of active substances.

/9

Table 3

Example for oral doses of combination preparations with calcium-antagonists for the therapy of different indications in humans

ACE-inhibitor	Active substance A	Daily dose of ACE-inhibitor	Daily dose of active substance A	Single doses of a) ACE-inhibitor b) active substance A	Frequency of application	Indication
Captopril	Oxidized/ reduced racemate or R- or S- lipoic acid	1-50 mg/day	300 mg-1.2 g	a) 25- 50 b) 100 - 400 mg	1- 2	Cardiac insufficiency, Diabetes mellitus Type II, nephropathy, arteriosclerosis, hypertension
Ramipril	Oxidized/ reduced racemate or R- or S-alpha-lipoic acid	1- 10 mg/day	300 mg-1.2 g	a) 1 - 5 mg b) 100 - 400 mg	1- 2	Hypertension, heart weakness
Lisonopril	Oxidized/ reduced racemate or R- or S- alpha-lipoic acid	1- 20 mg/day	300 mg-1.2 g	a) 1 - 12 mg b) 100 - 400 mg	1- 3	Heart weakness, hypertension
Enalapril hydrogen maleate	Oxidized/ reduced racemate or R- or S- alpha-lipoic acid	1- 20 mg/day	300 mg-1.2 g	a) 2.5 - 20 mg b) 100 - 400 mg	1-2	Cardiac insufficiency, Diabetes mellitus Type II, nephropathy, arteriosclerosis, hypertension
Perindopril-tert-butylamine	Oxidized/ reduced racemate or R- or S- alpha-lipoic acid	1-8 mg/day	300 mg-1.2 g	a) 1- 4 mg b) 100-400 mg	1- 2	Cardiac insufficiency, Diabetes mellitus Type II, nephropathy, arteriosclerosis, hypertension

The single dose of active substance A in combination, for instance, with ACE-inhibitor, captopril, can lie:

a) for oral administration between 50 mg - 3g, preferably 100 mg - 1.2 g.

b) for parenteral administration (for e.g. intravenous, intramuscular) between 50 mg - 3 g, preferably 100 mg - 2 g.

For instance, the daily dose of R- or S-alpha- lipoic acid in combination with Captopril can lie at 2- 40 mg per kg of weight in humans, the single dose being 1- 10 mg per kg of weight.

The daily dose can be 100 - 600 mg, therefore, the combination preparations contain preferably 100- 600 mg of R- or S- alpha-lipoic acid in a galenic formulation, whereby such a dose is administered preferably up to 4 times.

For the treatment, say 1 to 3 tablets with a content of 2.5 mg to 2 g of the active substance A can be given daily or say, an ampoule/ infusion bottle of 1 to 100 ml of content with 500 mg to 6 g of active substance A in combination with 1 - 20 mg of an ACE-inhibitor, say, lisinopril, is recommended daily one to three times in case of intravenous injection.

In case of oral administration, the minimum daily dose of active substance A in combination with an ACE-inhibitor

is, say, 200 mg; the maximum daily dose should not exceed 1.2 g in case of oral administration.

The single dose of an ACE-inhibitor in combination with the active substance A, can lie between 1mg- 50 mg, preferably 2 mg- 25mg, for instance, for ACE-inhibitor, captopril in case of oral administration.

/10

For the treatment, 1 to 2 tablets with a content of 0.5 mg to 5 mg of an ACE-inhibitor, for e.g. ramipril is recommended daily one to two times in the combination. For oral administration, the minimum daily dosage is 1.5 mg, for instance,s for an ACE-inhibitor, ramipril in the combination; the maximum daily dose should not exceed 10 mg of ramipril.

The daily oral dose of ACE-inhibitor, ramipril, in combination with the oxidized or reduced racemate or R- or S-enantiomer of alpha- lipoic acid can lie at, say, 1.25-10 mg/ per day in humans, the single dose of ACE-inhibitor, ramipril, in the combination is at 0.5 - 5 mg per day, whereby this dose can be administered suitably up to two times per day.

The pharmaceutical preparations of the combination of active substance A with oxyfedrin generally contain between 1 mg to 1.2 g as single dose, preferably 2 mg to 800 mg of

R- and/or S-alpha-lipoic acid, for instance, in combination with preferably 4- 48 mg, especially 8 to 24 mg of oxyfedrin. The obtained effective range/ kg of body weight must lie between 1.5 and 200 mg, preferably between 4 and 100 mg, especially between 8 and 70 mg/kg for the R- or S-form of alpha- lipoic acid and for instance, for oxyfedrin, between 4- 48 mg, preferably 8-24 mg, especially between 8-16 mg. The active substances must be released slowly from the preparations.

Table 4

Example for oral doses for therapy of angina pectoris in humans

Substance of Claim 6	Substance of Claim 1	Daily dosage of substance of Claim 1	Daily dosage of substance of Claim 2	Single doses of substance of a) Claim 6 b) Claim 1	Frequency of application
Oxyfedrin	Oxidized/ reduced racemate or R- or S-enantiomer of alpha-	4- 48 mg/ d	300 mg- 1.2 g	a) 4 -24 mg b) 100- 400 mg	1-3

	lipoic acid				

The single dose of active substance of combination partner according to Claim 1 in combination with oxyfedrin can lie in the following range for R- enantiomer of alpha-lipoic acid:

a) for oral administration between 5 - 300 mg, especially 30 mg - 240 mg, especially 30 mg -150 mg.

b) for parenteral administration (for e.g. intravenous) between 10 -250 mg, preferably 20- 150 mg, especially 30 -90 mg.

The doses according to a) to c) can be administered, for instance, one to 4 times, preferably one to two times daily.

The single dose of active substance of combination partner according to Claim 6 in the combination, for instance, with oxyfedrin can lie:

a) for oral administration between 4 - 48 mg, preferably 8 - 24 mg.

b) for parenteral administration (for e.g. intravenous, intramuscular) between 4 -48 mg/day, preferably 0.3 mg/kg of body weight/ h mg/hour.

The daily dose of R- and/or S-alpha- lipoic acid in the combination can lie for instance with oxyfedrin at 4-48 mg for humans; the single dose for example, at 4- 24 mg, whereby this dose is administered suitably up to 3 times per day.

The daily dose can be preferably, for instance, 100 - 600 mg. Therefore, the drugs preferably contain 100-600 mg of R- and/or S-alpha-lipoic acid in a galenic formulation, whereby such a dose is preferably administered up to 3 times. For the treatment, 1 to 3 tablets with a content of 5 mg to 1.2g of active substance of Claim 1 can be administered three times daily or for instance, an ampoule/infusion bottle of 1 to 100 ml of content with 250 mg to 800 mg of active substance of Claim 1 in combination with 0.1 -10 mg/hour of active substance of Claim 2 is recommended daily once in case of intravenous injection.

/11

In case of a product for separate usage, it is also possible not to administer both the combination partners simultaneously. In such cases, for example, oxyfedrin can be administered intravenous and R- and/or S-alpha-lipoic acid can be administered as continuous infusion.

The general dosage range for the combination of the oxyfedrin mentioned above with R- and or S-alpha- lipoic acid

for the preventive effect in angina pectoris can be:

4- 24 mg /day of oral oxyfedrin, in combination with 1- 100 mg/kg of R- or S-enantiomer of alpha- lipoic acid;

For the coronary- therapeutic effect can be:

4- 48 mg/day of oral oxyfedrin in combination with 1- 100 mg/kg of R- or S-enantiomer of alpha- lipoic acid,

For the anti-anginal effect can be:

8- 48 mg/day of oral oxyfedrin in combination with 1 -100 mg/kg of R- or S-enantiomer of alpha-lipoic acid.

The combinations with oxyfedrin and the optical isomers of alpha-liponic acid show, for instance, a good coronary-relaxing, anti-ischemic, heart insufficiency-therapeutic effect for the following trial models:

For testing of preventive or therapeutic effect:

1) in vitro: isolated guinea pig- rabbit aorta or isolated right or left auricle of guinea pig.

For testing of preventive or therapeutic effect:

2) in vivo: dog, domestic pig, model: coronary stenosis with the help of balloon-tipped catheter methods with subsequent, histological trial for reducing size of infarction or occurrence of infarction.

The pharmaceutical preparations that contain oxyfedrin as active substance in combination with R-alpha- lipoic acid or S-alpha-lipoic acid, can be formulated say, in the form of aerosols, tablets, capsules, pills or sugar-coated pills, granulates, pellets, medical strips, solutions or emulsions, whereby the active substances can be combined, if necessary, with the relevant excipients.

For instance, the R-alpha-lipoic acid and the S-alpha-lipoic acid in combination with oxyfedrin can be applied especially in the form of a solution, for instance, peroral, topical, parenteral (intravenous, intra-articular, intramuscular, subcutaneous), inhalative, transdermal.

In case solutions are used, the optical isomers of alpha- lipoic acid and the oxyfedrin contained in the combination are used preferably in the form of a salt.

The doses specified above always refer to combinations with oxyfedrin with, for e.g., free optical isomers of alpha-lipoic acid. In case the optical isomers of alpha-lipoic acid is used in the form of a salt, the specified doses/ dose ranges are to be increased correspondingly because of higher molar-weight.

In the combination of the invention consisting of active substance A and at least one organic nitrate, calcium- antagonists, ACE-inhibitor or oxyfedrin, both

components can exist as a mixture. Generally, the components exist separately in a galenic formulation.

For instance, one component can exist as a tablet or coated tablet, while the other component as powder, both in a capsule and vice versa one component in the form of medical strips or aerosols or pellets, the other as powder, sugar-coated pills or tablets and vice versa and whereby, both the forms can exist, say, in a capsule; or in the form of multi-layered tablets or coated tablets.

The combination according to the invention can exist even as a product in which both the individual active substances exist in completely separated formulations, whereby, the active substance A or even both the active substances are contained in ampoules and/or infusion bottles, such that even a separate or a staggered administration is possible.

In case such completely separated formulations exist, these are to be coordinated with each other and must contain the respective active substances in the dosing unit in the same quantity and appropriate weight ratio in which they can exist in the combined mixture.

For a product with separate usage, it is also possible not to administer both the combination partners simultaneously. In such cases, an organic nitrate can be

administered intravenous and the R- and/or S-alpha- lipoic acid can be administered as continuous diffusion.

The general dosage range for the organic nitrates, such as glyceroltri-nitrate, isosorbitdi-nitrate or 5- isosorbit mono-nitrate with the active substance A, such as R- or S-alpha-lipoic acid can be

for the preventive effect in angina pectoris:

-0.8- 2.5 mg /day of oral glyceroltri-nitrate in combination with 1- 100 mg/kg of R- or S-enantiomer of alpha- lipoic acid;

for the coronary- therapeutic effect:

-2.5 - 40 mg/day of oral isosorbitdi-nitrate in combination with 1- 100 mg/kg of R- or S-enantiomer of alpha- lipoic acid,

for the anti-anginal effect:

- 10- 40 mg/day of oral 5-isosorbitmono-nitrate in combination with 1 -100 mg/kg of R- or S-enantiomer of alpha-lipoic acid.

/12

The general dosage range for the combinations of calcium- antagonists with R- or S-alpha-lipoic acid can be for the neuroprotective effect:

30- 90 mg /day of oral nimodipin in combination with 1-100 mg/kg of R- or S-enantiomer of alpha-lipoic acid.

for the anti-hypertension effect:

40- 360 mg/day of oral verapamil in combination with 1-100 mg/kg of R- or S-enantiomer of alpha-lipoic acid.

for the coronary-therapeutic effect:

60- 180 mg /day of oral diltiazem in combination with 1-100 mg/kg of R- or S-enantiomer of alpha-lipoic acid.

for the anti-anginal effect:

5- 15 mg /day of oral nifedipin in combination with 1-100 mg/kg of R- or S-enantiomer of alpha-lipoic acid.

for the anti-diabetic effect:

40- 240 mg /day of oral verapamil in combination with 1-100 mg/kg of R- or S-enantiomer of alpha-lipoic acid.

For instance, the preferred daily dose in the combination for calcium-antagonist, nimodipin is 90 mg orally and parenteral for nimodipin 50 mg/day intravenous and for R-alpha- lipoic acid and also for S-alpha- lipoic acid 80 mg for parenteral administration and 200 mg for the oral form.

The dosage unit of combination preparations with a calcium- antagonist, such as nimodipin in combination with the optical enantiomers of alpha-lipoic acid or a therapeutically usable salt of the same (either R-form or S-form) can contain, for instance:

a) for oral administration:

10 to 1200 mg, preferably 20 to 600 mg of optical enantiomers of alpha-lipoic acid in combination with nimodipin 0.1 to 30 mg, preferably 2 to 30 mg. The doses can be administered one to four times, preferably one to three times daily. However, a total dosage of optical enantiomers of alpha-lipoic acid should not exceed 1200 mg and for instance, of calcium- antagonist, should not exceed 360 mg per day.

b) For parenteral administration (for example, intravenous, intramuscular or intra-articular):

10 to 600 mg, preferably 15 to 500 mg of optical enantiomers of alpha- lipoic acid in the combination 1-50 mg/day intravenous, preferably 3- 40 mg/day of body weight, especially 10- 30 mg/day intravenous.

The doses can be administered for instance one to four times, preferably one to three times daily.

Obviously, even galenic preparations can be manufactured which contain two to four times the above mentioned dosage units. The following especially contain:

- tablets or capsules contain 20 to 800 mg of active substance A in combination with, for instance, a calcium- antagonist, nimodipin, 1-30 mg,

- pellets, powder or granulate contain 5 to 600 mg of active substance A in combination with the calcium-antagonist, nimodipin 1-30 mg.
- Suppositories contain 20 to 300 mg of active substance A in combination with for instance 1-30 mg of nimodipin

In case the calcium-antagonist is used in combination with R- or S-alpha- lipoic acid in the form of its salts, the halogen can be used even in excess, that means, in a higher quantity than equimolar quantity.

The general dosage range for the combinations with ACE-inhibitors with R- or S-alpha-lipoic acid can be
for the cardio-cytoprotective effect:
12.5- 50 mg /day of oral captopril in combination with 1-100 mg/kg of R- or S- alpha-lipoic acid.
for the anti-hypertension effect:
1.25- 10 mg/day of oral ACE-inhibitor, ramipril, in combination with 1- 100 mg/kg of R- or S-alpha- lipoic acid.

The daily doses of the administrative forms of the combinations according to the invention for the cardio-cytoprotective and/or anti-hypertension effect contain, for

instance, preferably 1- 20 mg of lisinopril in combination with 0.1 to 600 mg, preferably 15 to 400 mg of R- or S-lipoic acid.

According to the invention, a daily dosage of combinations consisting of the above mentioned ACE-inhibitors and the optical enantiomers of alpha- lipoic acid of 5 - 50 mg of captopril, preferably 5- 25 mg and 10-600 mg of enantiomers, can be administered.

The maximum daily dosage for the cardio-cytoprotective and anti-hypertension effect should not exceed 1.2 g for the racemate or the R-or S-alpha-lipoic acid and should not exceed 50 mg for captopril.

The maximum daily dosage for the cardio-protective should not exceed 10 mg orally for the combination of ACE-inhibitor, ramipril with the R-or S-enantiomers of alpha-lipoic acid for ramipril and should not exceed 1.2 g for the enantiomers.

/13

The daily doses can be a single-dose administration of the total quantity or as 1- 3, especially 1- 2 partial doses per day. Generally, an administration of 1- 3 times daily is preferred.

In case solutions are used, the optical enantiomers of alpha- lipoic acid and the organic nitrates, calcium-

antagonists, ACE-inhibitors or oxyfedrin contained in the combination, are preferably used in the form of a salt.

The combination preparations according to the invention can be used even for the treatment of animals.

Generally, the oral single dose in combination lies between 2 mg/kg and 100 mg/kg of body weight for the active substance and between 0.01 and 1 mg/kg of body weight for the ACE-inhibitor for the treatment of heart insufficiency, diabetes mellitus type II, nephropathy, arteriosclerosis in horses and cattle.

The parenteral dose in the combination contains about 0.5 and 50 mg/kg of body weight of active substance A and approximately between 0.005 and 1 mg/kg of body weight of an ACE-inhibitor.

All the doses given above of the active substance A and of the organic nitrates, calcium- antagonists or ACE-inhibitors do not relate to the pharmaceutically usable salts. In case, these are used in the form of a salt, the specified doses/ dosage range are to be increased appropriately because of the higher molar weight.

The pharmaceutical combinations according to the invention in combination with organic nitrates can be used especially for the therapy and treatment of angina pectoris, left ventricular insufficiency, for treatment of

sub-acute and acute cardial pulmonary edema, pulmonary hypertension and of organic nitrate tolerance.

The indications for the combination preparations with a calcium-antagonist can be:
Diabetes mellitus, degenerative diseases of central nervous system, acute ischemic conditions, myocardial infarction, nerve degeneration (neureo-degenerative processes) cerebral neuropathy, Morbus Alzheimer, coronary insufficiency, angina pectoris, atrial fibrillation/atrial flutter with tachyarrhythmia, tachycardiac rhythm disturbances such as paroxysmal supraventricular tachycardia, Raynoud-syndrome, therapy of cardiac infarction, hypertension, hypertonic crisis, prophylaxis and therapy of ischemic neurological deficits because of cerebral vasospasm after subarachnoid hemorrhage.

The pharmaceutical combinations with ACE-inhibitors can be used especially for the treatment of hypertension, hypertonic crisis, cardiac insufficiency, diabetes mellitus type II, nephropathy, cerebrovascular events, nephropathy, cardiomyopathy and arteriosclerosis.

The pharmaceutical combination preparations with oxyfedrin can be used for prevention and treatment of angina pectoris, left ventricular insufficiency, for treatment of coronary insufficiency, partial AV- conduction

defects, subsequent states of myocardial infarction and autonomous cardial neuropathy.

The production of combination preparations according to the invention takes place in a known way, whereby the customary pharmaceutical excipients can be used. For example, those substances that are recommended or specified in the following literature as excipients for pharmaceutics, cosmetics and related fields, can be used as excipients:

Ullmanns Encyclopedia of technical Chemistry, Volume 4 (1953), Page 1 to 39;

Journal of Pharmaceutical Sciences, Volume 52 (1963), Page 918 onwards,

H. v. Gzetsch- Lindenwald, Excipients for pharmaceutics and related fields, Pharm. Ind. Book 2 (1961), Page 72 onwards.

Dr. H. P. Fiedler, Lexicon of excipients for pharmaceutics, cosmetics and related fields, Cantor KG, Aulendorf in Württemberg (1989).

The pharmaceutical and galenic handling of organic nitrates, such as glyeroltri-nitrate, isosorbit-di-nitrate or 5- isosorbitmono-nitrate and R- and/or S-alpha-lipoic acid is undertaken according to the usual standard methods.

The combinations according to the invention can be produced as follows:

200 mg of R- and/or S-alpha- lipoic acid or/and excipients are mixed well in 250 ml of aqueous isosorbitdi-nitrate or in 200 ml of 5-isosorbitmono-nitrate by stirring or homogenization (for e.g. with the help of customary mixing devices) (clear solution) whereby it is operated generally at temperatures between 20 and 50°C, preferably 20 to 40°C.

Examples for excipients are gelatins, natural sugars such as sucrose or lactose, lecithin, pectin, starches (for example, cornstarch or amyloses), cyclodextrins and cyclodextrin derivatives, dextran, polyvinyl pyrrolidone, polyvinyl acetate, acacia, alginic acid, tylose, talcum, lycopodium, silicic acid (for example, colloidal), cellulose, cellulose derivatives (for example, cellulose ether, for which the cellulose- hydroxyl groups are partially etherified with lower saturated aliphatic alcohols and/or lower saturated aliphatic oxyalcohols, for example, methyloxypropyl cellulose, methyl cellulose, hydroxypropyl- methyl cellulose, hydroxy propylmethyl-cellulose phthalate), fatty acids as well as magnesium-, calcium- or aluminum salts of fatty acids with 12 to 22 C-atoms, especially of saturated (for example, stearates), emulsifiers, oils and fats, especially vegetable (for example, peanut oil, castor oil, olive oil, sesame oil,

cottonseed oil, corn oil, wheat germ oil, sunflower seed oil, cod liver oil, even hydrated); glycerin esters and polyglycerin esters from saturated fatty acids $C_{12}H_{24}O_2$ to $C_{18}H_{36}O_2$ and their mixtures, whereby the glycerin- hydroxy groups are completely or only partially esterified (for e.g. mono-, di- and triglycerides) pharmaceutically acceptable mono- or multivalent alcohols and polyglycols such as polyethylene glycols (molecular weight range for example 300 to 1500) and also derivatives hereof, polyethylene oxide, esters of aliphatic saturated or unsaturated fatty acids (2 to 22 C-atoms, especially 10 - 18 C-atoms) with mono-valent aliphatic alcohols (1 to 20 C-atoms) or multivalent alcohols such as glycols, glycerin, diethylene glycol, pentaerythritol, sorbitol, mannite and the like, which can even be etherified, esters of citric acid with primary alcohols, acetic acid, urea, benzyl benzoate, dioxolane, glycerin formals, tetrahydrofurfuryl alcohol, polyglycol ether with C1- C12-alcohols, dimethyl acetamide, lactamide, lactate, ethyl carbonate, silicones (especially medium-viscous polydimethyl siloxanes), calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, magnesium carbonate and the like.

/14

Other auxiliary materials can be substances that cause disintegration – so-called exploders- such as cross-linked polyvinyl pyrrolidone, sodium carboxy methyl starches, sodium carboxy methyl cellulose or micro-crystalline cellulose. Likewise, known coating materials can be used. Examples of such are: polymers as well as copolymers of acrylic acid and/or methacrylic acid and/or their esters; copolymers from acrylic acid esters and methacrylic acid esters with low content of ammonium groups (for e.g. Eudragit® RS), copolymers from acrylic acid esters and methacrylic acid esters and trimethyl ammonium methacrylate (for e.g. Eudragit RL); polyvinyl acetate; fats, oils, wax, fatty alcohols; hydroxypropylmethyl cellulose phthalate or -acetate succinate; cellulose- acetate phthalate- starch-acetate phthalate as well as polyvinylacetate phthalate; carboxymethyl cellulose; methyl cellulose phthalate, methyl cellulose succinate, -phthalate succinate as well as methyl cellulose- phthalic acid half esters; zein; ethyl cellulose as well as ethyl cellulose succinate; shellac, gluten; ethylcarboxyethyl cellulose; ethacrylate-maleic acid anhydride-copolymer; maleic acid anhydride-vinyl methyl ether-copolymers; styrene- maleic acid-copolymes; 2-ethyl-hexyl-acrylate maleic acid anhydride; crotonic acid-vinyl acetate-copolymer; glutaminic acid/ glutaminic acid ester

copolymer, carboxymethyl ethyl cellulose glycerine-mono-octanoate, cellulose acetate succinate and polyarginine.

Plasticizing agents for coating materials can be: Citric acid ester and tartaric acid ester (acetyltriethyl citrate, acetyltributyl, tributyl, triethyl citrate), glycerin and glycerin ester (glycerin diacetate, -triacetate, acetylated monoglycerides, castor oil), phthalic acid ester (dibutyl, diamyl, diethyl, dimethyl, dipropyl-phthalate), di-(2-methoxy- or 2-ethoxy ethyl)-phthalate, ethylphthalyl- glycolate, butylphthalylethyl glycolate and butyl glycolate; alcohols (propylene glycol, polyethylene glycol of different chain lengths), adipates (diethyl- adipate, di-(2- methoxy- or 2-ethoxy ethyl)-adipate); benzophenone; diethyl- and dibutylsebacate, dibutylsuccinate, dibutyltartrate; diethylene glycol dipropionate; ethyleneglycol diacetate, -dibutyrate, -dipropionate; tributyl phosphate, tributyrin, polyethylene glycol sorbitan monooleate (polysorbates such as polysorbate 80) and sorbitan monooleate.

For the manufacture of solutions or suspensions, water or physiologically compatible organic solvents can be used, for example

Alcohols (ethanol, propanol, isopropanol, 1,2- propylene glycol, polyglycols and their derivatives, fatty alcohols,

partial esters of glycerin), oils (for e.g., peanut oil, olive oil, sesame oil, almond oil, sunflower- oil, soyabean oil, castor oil), paraffins, dimethyl sulfoxide, triglycerides and the like.

Non-toxic parenteral- compatible diluents or solvents can be used for injectable solutions or suspensions, for example: water, 1,3-butandiol, ethanol, 1,2-propylene glycol, polyglycols mixed with water, glycerol, Ringer's solution, isotonic sodium chloride solution or even solidified oils including synthetic mono- or diglycerides or fatty acids such as oleic acid.

Known and customary solubilizers, or even emulsifiers can be used for the manufacture of preparations.

Examples of solubilizers and emulsifiers are: polyvinylpyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, phosphatide, such as lecithin, acacia, tragacanth, polyoxyethylated sorbitan monooleate and other ethoxylated fatty acid esters of sorbitan, polyoxyethylated fats, polyoxyethylated oleotriglycerides, -linolizated oleotriglycerides, polyethylene oxide-condensation products of fatty alcohols, alkyl phenols or fatty acids or even 1-methyl-3- (2-hydroxyethyl) imidazolidone- (2).

In this context, polyoxyethylated means that the relevant substances contain polyoxyethylene chains, their degree of polymerization generally lies between 2 and 40 and especially between 10 and 20.

Such polyoxyethylated substances can be obtained, for instance, by conversion of hydroxyl group-contained compounds (for instance, mono- or diglycerides or unsaturated compounds such as those that contain oleic acid radicals) with ethylene oxide (for example, 40 moles of ethylene oxide per one mole of glyceride).

Examples for oleotri-glycerides are olive oil, peanut oil, castor oil, sesame oil, cotton seed oil, corn oil.

Moreover, preservatives, stabilizers, buffer substances, flavor correcting agents, sweeteners, colorants, antioxidants and chelating agents and the like can be added.

Examples of chelating agents are:

Chelate formers such as ethylene diamino-tetra acetic acid, nitrilotri acetic acid, diethylene triamine pentaacetic acid and also their salts. Further, even those that contain active substance B in combination with, for instance, R- or S-alpha-lipoic acid in a cavity can be used as chelating agents. Examples for these are urea, thiourea, cyclodextrins, amylose. If necessary, it is possible to

stabilize the active substance molecule with physiologically compatible bases or buffers to a pH-range of about 6 to 9. Generally, as far as possible, neutral to weak basic (up to pH 8) pH-value is preferred.

Antioxidants that may be used are, for instance, sodium sulfite, sodium hydrogen sulfite, sodium metabisulfite, ascorbic acid, ascorbyl palmitate, -myristate, -stearate, gallic acid, gallic acid- alkyl ester, butyl hydroxyanisol, nordihydroguaiacic acid, tocopherols as well as synergists (substances that bind heavy metals by complex formation, for example, lecithin, ascorbic acid, phosphoric acid ethylene diaminotetra-acetic acid, citrate, tartrates). The addition of synergists considerably increases the anti-oxygenic effect of anti-oxidants.

Preservatives that may be used are, for example, sorbic acid, p-hydroxy benzoic acid ester (for example, lower alkyl ester), benzoic acid, sodium benzoate, trichlorisobutyl alcohols, phenols, cresols, benzethonium chloride, chlorohexidine and formalin derivatives.

/15

Examples

Example 1

Tablets with 50 mg of S- or R-alpha-lipoic acid and 8 mg of oxyfedrin

250 g of S-alpha-lipoic acid and 40 g of oxyfedrin are evenly grounded with 760 g of micro-crystalline cellulose. After sieving the mixture, 250 g of starch (starch 1500/ Colorcon), 682.5 g of lactose, 15 g of magnesium stearate and 2.5 g of highly dispersible silicon dioxide are mixed together and the mixture is pressed into tablets weighing 400.0 mg.

A tablet contains 50 mg of S-alpha- lipoic acid and 8 mg of oxyfedrin.

In the same way, tablets with 50 g of R-alpha-lipoic acid can be produced, wherein in place of 250 g of S-alpha-lipoic acid, the same quantity of R-alpha-lipoic acid is used.

If necessary, tablets can be provided with gastric juice-soluble or gastric juice permeable film coating using conventional methods.

Example 2

Capsules with 250 mg of R- or S-alpha-lipoic acid and 0.8 mg of glycerol trinitrate

250 g of R-alpha-lipoic acid are mixed with 8 g of glycerol trinitrate.

Subsequently, 1095.2 g of Miglyol®- neutral oil and 42 g of sorbitol syrup, 25 g of glycerol are then added hereto and the mixture is filled in size 00 capsules.

Miglyol® is a commercial mixture of medium-chained triglycerides.

A capsule weighing 1.42 g contains 250 mg of R- or S-alpha-lipoic acid and 0.8 mg of glycerol trinitrate.

Example 3

Suppositories with 50 mg of dihydrolipoic acid or with R- or S-alpha-lipoic acid and 30 mg of nimodipin

5 g of ascorbyl palmitate and 5 g of oxynex LM (E. Merck, Darmstadt) are suspended in 192 g of molten hard fat. Subsequently, 3 g of nimodipin and 5 g of dihydrolipoic acid are mixed together and the mixture is poured out into hollow cells of 2.3 ml after homogenization. Before sealing, the hollow cells are purged with nitrogen.

Hard fat is a mixture of mono-, di- and triglycerides of saturated fatty acids of $C_{10}H_{20}O_2$ to $C_{18}H_{36}O_2$.

Oxynex LM is a commercial additive for fats and fat-containing foodstuffs. It is a light brown, waxy mass which melts into a clear brown liquid when heated to 55°C and

contains tocopherol, ascorbyl palmitate, citric acid and lecithin.

A suppository weighing 2.1 g contains 50 mg of dihydrolipoic acid and 30 mg of nimodipin.

Suppositories with R- or S-alpha-lipoic acid can be produced in the same way, in which case, the same quantity of either R- or S-alpha-lipoic acid is used in place of dihydrolipoic acid.

Example 4

Capsules with 200 mg of dihydrolipoic acid or with R- or S-alpha-lipoic acid and 30 mg of nimodipin

200 g of R-alpha-lipoic acid are mixed with 30 mg of nimodipin.

Subsequently, 1065 g of Miglyol®- neutral oil and 100 g of sorbitol syrup, 25 g of glycerol are then added hereto and the mixture is filled in size 00 capsules. A capsule weighing 1.42 g contains 200 mg of R- or S-alpha-lipoic acid and 30 mg of nimodipin.

Miglyol® is a commercial mixture of medium-chained triglycerides.

Capsules with hydrolipoic acid or with S-alpha-lipoic acid are produced in the same way in which the same

quantity of either dihydrolipoic acid or S-alpha-lipoic acid is used instead of R-alpha-lipoic acid.

Example 5

Ampoules with 250 mg of R- or S-alpha-lipoic acid and 30 mg of calcium-antagonist, nimodipin in 10 ml

250 g of R-alpha-lipoic acid are dissolved along with 352.3 g of trometamol (2-amino (hydroxymethyl)-1,3-propandiol) in a mixture containing 8 liters of water for injection purposes and 200 g of 1,2-prophylene glycol under stirring. Subsequently, 30 g of calcium- antagonist, nimodipin, is dissolved in this preparation. The solution is filled up to 10 liters with water for injection purposes and subsequently, filtered through a membrane filter of pore width 0.2 μm with fiberglass pre-filter. The filtrate is filled up to 10 ml in sterilized 10 ml-ampoules under aseptic conditions.

An ampoule contains 250 mg of R-alpha-lipoic acid as trometamol salt and 30 mg of calcium-antagonist, nimodipin in 10 ml injection solution.

Ampoules can be produced with S-alpha-lipoic acid in the same way in which the same quantity of S-alpha-lipoic acid is used instead of R-alpha-lipoic acid.

/16

Example 6

Tablets with 50 mg of S- or R-alpha- lipoic acid and 30 mg of calcium-antagonist, nimodipin

250 g of S-alpha-lipoic acid and 150 g of calcium-antagonist, nimodopin are evenly grounded with 650 g of micro-crystalline cellulose. After sieving the mixture, 250 g of starch (starch 1500/ Colorcon), 682.5 g of lactose, 15 g of magnesium stearate and 2.5 g of highly dispersible silicon dioxide are mixed together and the mixture is pressed into tablets weighing 400.0 mg.

A tablet contains 50 mg of S-alpha- lipoic acid and 30 mg of calcium-antagonist, nimodipin.

In the same way, tablets with 50 mg of R-alpha-lipoic acid can be produced, wherein in place of 150 g of S-alpha-lipoic acid, the same quantity of R-alpha-lipoic acid is used.

If necessary, tablets can be provided with gastric juice-soluble or gastric juice permeable film coating using conventional methods.

Example 7

Capsules with 250 mg with R- or S-alpha-lipoic acid and 10 mg of Captopril

250 g of R-alpha- lipoic acid is mixed with 10 g Captopril.

Subsequently, 1050 g of Miglyol®- neutral oil and 85 g of sorbitol syrup, 25 g of glycerol are then added hereto and the mixture is filled in size 00 capsules.

Miglyol® is a commercial mixture of medium-chained triglycerides.

A capsule weighing 1.42 g contains 250 mg of R-alpha- or S-alpha-lipoic acid and 10 mg of Captopril.

Example 8

Tablets with 50 mg of S- or R-alpha-lipoic acid and 1.25 mg of ramipril

250 g of S-alpha-lipoic acid and 6.25 g of ramipril are evenly grounded with 792.5 g of micro-crystalline cellulose. After sieving the mixture, 250 g of starch (starch 1500/ Colorcon), 682.5 g of lactose, 15 g of magnesium stearate and 2.5 g of highly dispersible silicon dioxide are mixed together and the mixture is pressed into tablets weighing 400.0 mg.

A tablet contains 50 mg of S-alpha- lipoic acid and 1.25 mg of ramipril.

In the same way, tablets with 50 mg of R-alpha-lipoic acid can be produced, wherein in place of 250 g of S-alpha-

lipoic acid, the same quantity of R-alpha-lipoic acid is used.

If necessary, tablets can be provided with gastric juice-soluble or gastric juice permeable film coating using conventional methods.

Patent claims

1. Pharmaceutical combination preparations characterized in that they contain an alpha-lipoic acid or its metabolites and at least one organic nitrate, a calcium- antagonist, ACE- inhibitors or oxyfedrin as active substance A.
2. Pharmaceutical combination preparations according to Claim 1 characterized in that they contain alpha-lipoic acid, dihydrolipoic acid and their oxidized or reduced R- or S-enantiomers as well as metabolites of alpha- lipoic acid, such as 6,8- bisnorlipoic acid, tetranorlipoic acid as active substance A.
3. Pharmaceutical combination preparations according to Claim 1, characterized in that they contain at least one organic nitrate such as glycerol trinitrate, isosorbitdinitrate or 5-isosorbitmononitrate.
4. Pharmaceutical combination preparations according to Claim 1, characterized in that they contain at least

one calcium- antagonist of the type Verapamil, nifedipine, nimodipine, felodipine, isradipine, nitrendipine, nisoldipine, nicardipine, nivaldipine or diltiazem.

5. Pharmaceutical combination preparations according to Claim 1, characterized in that they contain at least one ACE-inhibitor of type captopril, lisinopril, perindropril-tert-butylamine, ramipril or enalapril hydrogen maleate.

6. Pharmaceutical combination preparations according to Claim 1, characterized in that they contain oxyfedrin.

7. Pharmaceutical combination preparations according to Claims 1 to 3, characterized in that 0.1 to 40 parts by weight of an organic nitrate is used for 1 to 1000 parts by weight of active substance A in the dosage unit of the combination.

8. Pharmaceutical combination preparations according to Claims 1 to 3, characterized in that the combinations contain 5-1200 mg, preferably 10- 800 mg of active substance A and 0.1 - 40 mg, preferably 0.8 -20 mg of an organic nitrate.

/17

9. Pharmaceutical combination preparations according to Claims 1 to 3, characterized in that the combinations

contain 1-1200 mg, preferably 2- 800 mg of active substance A and 0.1 - 40 mg, preferably 0.8 -20 mg of an organic nitrate.

10. Pharmaceutical combination preparations according to Claims 1, 2 and 4, characterized in that, 1 to 120 parts by weight of a calcium-antagonist is used for 1 to 1000 parts by weight of active substance A in the dosage unit of the combination.

11. Pharmaceutical combination preparations according to Claims 1,2 and 4, characterized in that the combinations contain 5-6000 mg, preferably 10- 3000 mg of active substance A and 5 - 120 mg, preferably 0.8 - 20 mg of a calcium antagonist.

12. Pharmaceutical combination preparations according to Claims 1,2 and 4, characterized in that the combinations contain 2-1000 mg, preferably 2- 800 mg of active substance A and 5 - 120 mg of a calcium antagonist.

13. Pharmaceutical combination preparations according to Claims 1,2 and 5, characterized in that 1 to 20 parts by weight of an ACE-inhibitor is used for 1 to 1000 parts by weight of active substance A in the dosage unit of the combination.

14. Pharmaceutical combination preparations according to Claims 1,2 and 5, characterized in that the combinations contain 5-6000 mg, preferably 10-3000 mg of active substance A and 1 - 20 mg of an ACE-inhibitor.

15. Pharmaceutical combination preparations according to Claims 1, 2 and 5, characterized in that the combinations contain 2-3000 mg, preferably 2- 1000 mg of active substance A and 1 - 20 mg of an ACE-inhibitor.

16. Pharmaceutical combination preparations according to Claims 1, 2 and 6, characterized in that, 0.1 to 40 parts by weight of oxyfedrin is used for 1 to 1000 parts by weight of active substance A in the dosage unit of the combination.

17. Pharmaceutical combination preparations according to Claims 1, 2 and 6, characterized in that the combination contains 5-1200 mg, preferably 10- 800 mg of active substance A and 4 - 48 mg of oxyfedrin.

18. Pharmaceutical combination preparations according to Claims 1, 2 and 6, characterized in that the combination contains 2-1200 mg, preferably 2- 800 mg of active substance A and 0.1 - 40 mg or especially 4-48 mg of oxyfedrin.

19. Pharmaceutical combination preparations according to Claim 1, characterized in that they contain, if necessary, additional pharmaceutical excipients and/or other additives.

20. Pharmaceutical combination preparations according to Claims 1 and 19, characterized in that they are administered in the form of tablets, capsules, pills, sugar-coated pills, aerosols, salves, creams, medical strips, suspension or solution.

21. Usage of combination preparations according to Claim 1 in combination with organic nitrates of Claim 3 for therapy and treatment of angina pectoris, left ventricular insufficiency, for treatment of sub-acute and acute cardial pulmonary edema, pulmonary hypertension and of organic nitrate tolerance.

22. Usage of combination preparations according to Claim 1 in combination with calcium-antagonist of Claim 4 for therapy of diabetes mellitus, nerve degeneration (neureo-degenerative processes) cerebral neuropathy, Morbus Alzheimer, coronary insufficiency, angina pectoris, atrial fibrillation/atrial flutter with tachyarrhythmia, tachycardiac rhythm disturbances such as paroxysmal supraventricular tachycardia, Raynoud-syndrome, therapy of cardiac infarction,

hypertension, hypertonic crisis, prophylaxis and therapy of ischemic neurological deficits because of cerebral vasospasm after subarachnoid hemorrhage.

23. Usage of combination preparations according to Claim 1 in combination with ACE-inhibitors of Claim 5 for treatment of essential hypertension, cardiac insufficiency, hypertension, hypertensive cardiomyopathy, myocardial insufficiency, diabetes mellitus type II, nephropathy, arteriosclerosis, nephropathy and cerebrovascular events.

24. Usage of combination preparations according to Claim 1 in combination with oxyfedrin for prevention and treatment of angina pectoris, left ventricular insufficiency, subsequent states after myocardial infarction, partial AV- conduction defects.

25. Method for manufacture of combination preparations according to Claim 1 characterized in that the active substance A and at least one organic nitrate, calcium- antagonist, ACE-inhibitor or oxyfedrin or their pharmaceutically usable salts are mixed or homogenized with pharmaceutical excipients and/or other additives at temperatures between 0 and 120°C, preferably 20 to 80°C, and the mixture so obtained is filled in hollow cells of appropriate size

or in capsules or granulated and then, if necessary, pressed into tablets by adding other customary auxiliary substances or filled in capsules.

26. Method for manufacture of combination preparations according to Claim 1 characterized in that the active substance A and at least one organic nitrate, calcium- antagonist, ACE-inhibitor or oxyfedrin or their pharmaceutically usable salts are dissolved in water, physiologically harmless alcohols, oils or dimethyl sulfoxide or mixtures thereof at temperatures between 20 and 100°C, if necessary, in the presence of chelating agent and/or of emulsifier, and the solutions and suspensions so obtained are filled up.

/18

27. Pharmaceutical combination preparations according to Claim 1, characterized in that the active substance A and at least one organic nitrate, calcium-antagonist, ACE-inhibitor or oxyfedrin exist in the same dosage form for administration at the same time.

28. Pharmaceutical combination preparations according to Claim 1, characterized in that the active substances A and B exist in different dosage forms for administration at the same time.